the data cannot always be assessed prior to a detailed review, and the review can occur only after the application is submitted. The dispute resolution procedures described in the final rule would be applicable to foreign data issues, and this would include referral of those issues, at FDA's option, to an advisory committee.

117. Several comments argued that FDA should be required to accept foreign data unless the agency can demonstrate that the data should not be accepted for some valid scientific or medical reason. These comments also urged that the final rule require FDA to explain in writing its refusal to accept foreign data to ensure that duplicative domestic studies would not be required except for good reason.

FDA disagrees with these comments to the extent that they suggest that the burden of proof should be on the agency to show why foreign data are inadequate. Rather, the final rule, like the proposal, places the burden on the applicant to demonstrate to the agency's satisfaction that the foreign data are sufficient, by themselves, for approval. The agency emphasizes that there are no hidden criteria for evaluating the acceptability of foreign data. FDA will approve an application that relies upon foreign data unless one of the grounds identified in the statute or regulations for refusing to approve an application applies. If the agency concludes that the application is not approvable, it will give the applicant the basis for the conclusion in a deficiency letter or a not approvable letter and, if the applicant wishes, in a notice of opportunity for hearing. Thus, a mechanism already exists under which FDA will explain to the applicant, in writing, its reasons for refusing to approve an application based solely on foreign data.

Approvable and Not Approvable Letters (§ § 314.110 and 314.120)

118. One comment understood an approvable letter to mean that, except for matters specifically identified in it, the information already submitted in the application is acceptable and will not be further reviewed, and, except for safety update reports, no more information will be required before approval. Another comment suggested that an applicant's unconditional agreement to comply with conditions in an approvable letter should be sufficient for the agency to approve the application immediately, and that no extension of the review period or additional submission should be needed.

FDA agrees that an approvable letter means that FDA, at the time the letter issues, intends to approve the application if the applicant submits the requested data or information. Nevertheless, the issuance of an approvable letter does not preclude FDA from reexamining any part of the application in light of the applicant's response to the letter, or any other data or information before the agency bearing on the application. Although applicants have long argued that FDA should not re-review parts of an application that it has once determined are acceptable (and FDA agrees that in most cases another review is unwarranted), the agency considers all parts of an application to market a new drug to be interrelated, so that a change in one part may affect other parts of the application. Thus, FDA will continue to consider the impact of new submissions on other sections of the application. With respect to the second comment, except in the situation where the only changes to be made are editorial or affect minor aspects of the draft labeling, FDA believes that responses to approvable letters must be reviewed by FDA prior to final approval of the application because the information submitted could affect the safety or effectiveness of the drug.

119. Several comments argued that 10 days is inadequate time for an applicant to respond to an approvable or not approvable letter and that an applicant should have at least 30 days from the date of receipt of the letter, with an opportunity for extensions of time for good cause. According to these comments, in many cases the applicant must gather a number of experts in several disciplines together to consider FDA's letter, recommend a course of action to management, and obtain a management decision on it.

FDA does not believe that the 10-day period for a response to an approvable or not approvable letter will necessarily be insufficient for applicants to determine whether they will seek to amend an application, or request that the agency issue a notice of opportunity for hearing. In some cases, applicants may have enough information regarding the status of their applications prior to receipt of the action letter to know whether anticipated deficiencies are amenable to remedial action by the firm, or whether they are so great as to require pursuit of an administrative hearing. More importantly, however, the primary purpose in revising this section of the regulations was to provide for agency action within the 180-day time frame specified by the act. In meeting its obligations to reach a decision within the statutory period, the agency has undertaken to observe strict time limits in the review of new drug applications. As meeting the statutory period will necessitate industry responses to agency action, reasonably strict time limits are appropriately applied to industry as well.

Nonetheless, the agency recognizes that in many cases applicants may find 10 days inadequate to respond to an approvable or not approvable letter. For example, the applicant may wish to delay such a decision until after it has had an opportunity to meet with FDA officials in an "end-of-review conference," as provided in § 314.102(d). Thus, FDA has amended the regulations to permit applicants to respond by agreeing to an extension of the approval time, as provided under section 505(c) of the act. Moreover, the regulation makes clear that FDA will honor any reasonable request for such an extension. The 10-day provision, therefore, should not create any undue hardship on applicants. This resolution of the issue presented by the comments accommodates both the comments' concern and the agency's need to adhere to the 180-day period provided for by statute. The agency considered shortening the time necessary to prepare a notice of opportunity for hearing to accommodate a longer period for an applicant's response to an action letter, but has determined that it is impracticable to shorten the period in which a notice of opportunity for hearing can be prepared to less than 50 days.

120. Several comments objected to the automatic 45-day extension of the review period when an applicant decides to file an amendment in response to an approvable letter. Two comments suggested a provision permitting extensions of "up to" 45 days, while two other comments suggested that 30 days is appropriate. Another comment suggested that the agency should advise the applicant in writing about what the time will be, but that it should be no more than 45 days.

FDA selected 45 days as the maximum time for FDA action on the applicant's response to an approvable letter because it believes it will generally take that long to review the applicant's response, prepare an approval letter recommendation, and issue the approval. If that process is completed sooner, the approval letter will issue in less than 45 days. The agency believes, however, that a significant number of applications would fail to meet the 30-day time period suggested by the comments and, thus, the agency has not adopted it. In addition, FDA believes that the requested change would distract reviews from evaluating the submission by requiring them to decide on a feasible extension shorter than 45 days, and thus would be more likely to disrupt the review process than to benefit applicants.

Refusal To Approve an Application (§ 314.125)

121. Noting that the first six reasons for refusing to approve an application rephrase the statutory grounds in section 505(d) of the act, one comment argued that the agency failed to assert a legal basis for the remaining eight reasons and that, accordingly, those eight reasons should be deleted.

FDA does not agree. The agency views each of the grounds stated to be within the scope of section 505(d) of the act. Each of the grounds asserted, both those stated explicitly in section 505(d) of the act and those not, reflect FDA's authority to prohibit marketing of drug products that do not comply with regulatory standards that marketed drugs be safe, effective, and properly labeled. FDA would view as unreasonable a requirement that, for a ground not specifically listed in section 505(d) of the act but included in § 314.125, it must approve such a product and immediately take action against it under some other section of the act. Rather, FDA views it as a reasonable exercise of its rulemaking authority to include within the reasons for refusing to approve an application under section 505(d) of the act reasons consistent with the agency's authority to establish marketing requirements for, or withdraw approval of, new drugs. Moreover, FDA believes that the list of additional grounds in the regulations will give applicants more specific notice of the kinds of grounds on which the agency will refuse to approve applications.

122. One comment objected to FDA removing the characteristics of an adequate and well-controlled study from this part of the current regulation, fearing that it suggested a predisposition of FDA not to involve qualified experts in the evaluation of clinical investigations to determine whether substantial evidence of effectiveness exists.

FDA disagrees and concludes that changing the location in the regulation of the provision in question will have no substantive effect on the agency's refusal to approve an application for a lack of substantial evidence of effectiveness, nor will it affect the role of experts in the review process. The regulation retains almost verbatim the grounds cited in the act for refusal to approve an application because of a lack of substantial evidence of effectiveness. The discussion of the characteristics of adequate and well-controlled studies, although placed in a separate section and somewhat revised in language, is still comprehensive in nature and can be cited by the agency in any decision not to approve an application.

123. One comment urged FDA to exempt minor deviations in proposed labeling when determining whether it complies with the requirements for labels and labeling in 21 CFR Part 201. Other comments objected to the suggestion that bioavailability or bioequivalence data are intended to show that a drug is safe or effective, while one comment asked FDA to retain the wording from the current rule under which approval may be refused if the data in the application do

not meet the requirements in 21 CFR Part 320. One comment stated that it is unnecessary to include the provision for refusal to approve an application if a deficiency noted in a refusal-to-file letter had not been corrected. Finally, one comment objected to FDA's assertion that it can refuse to approve an application if the applicant does not permit an FDA investigator to inspect the facilities, controls, and any records relevant to the application. The comment contended that that provision goes well beyond FDA's inspectional authority in section 704(a) of the act *(21 U.S.C. 374*(a)).

Although FDA has reaffirmed its policy to approve an application if editorial or similar minor changes in draft labeling will be made in the final printed labeling, FDA cannot sanction deviations from the standards in Part 201 that would cause the drug to be misbranded. The agency agrees that the current wording under which FDA may refuse to approve an application if bioavailability and bioequivalence data do not meet the requirements in Part 320 is more informative than the proposed wording and the agency has revised the regulation to retain it. Because an applicant can file an incomplete application over protest, FDA sees a need to retain the provision permitting the agency to refuse to approve an incomplete application. Finally, FDA is obligated to refuse to approve an application if it believes (in the absence of an inspection that would demonstrate otherwise) that the facilities and controls are inadequate or the information in the application based on records helds by the applicant is insufficient to determine that the drug is safe or effective. An inspection under this provision derives from section 505 of the act and the result of an inspection refusal is the possibility that the agency will not have adequate information to approve the application. The agency notes that although it has suggested it would refuse to consider a particular study if records of the study could not be inspected, it does not take the position that it will reject an entire application solely because a part of the records could not be inspected (so long as they were not considered essential to the approval).

Adequate and Well-Controlled Studies (§ 314.126)

124. Several comments objected to FDA's statement that the characteristics set forth in its regulations are recognized by the scientific community as the "essentials" of an adequate and well-controlled study. Comments suggested that the listed characteristics do not uniquely define such a study. A study may, according to comments, include an additional characteristic or lack one or more of the listed characteristics and still be adequate and well-controlled. For example, one comment suggested that the characteristics of an adequate and well-controlled study should include an explanation of the difference between the study's objectives and its results so that deviations from the original objectives can be justified, while other comments urged that the characteristics should not include the method of selection of subjects, the method of assigning subjects to treatment groups, the measures taken to minimize bias on the part of analysts of the data, the method of assessment of subjects' responses, or an assessment of a study's ability to detect more than a "clinically significant" difference between treatments. Another comment suggested that study characteristics should appear in a guideline instead of a regulation. That change, according to the comment, would recognize that appropriate alternative characteristics exist, and would provide clinical investigators and sponsors with flexibility to adopt them without first obtaining a waiver.

FDA has long considered the characteristics listed in the regulation as the essentials of an adequate and well-controlled study, and the proposal modified these characteristics only slightly. In general, the regulation on adequate and well-controlled studies has two overall objectives: (1) To allow the agency to assess methods for minimizing bias; and (2) to assure a sufficiently detailed description of the study to allow scientific assessment and interpretation of it. Many of the characteristics identified in the regulation are relevant to the second objective (rather than the first, as implied by the comments) and are needed by the agency to conduct a proper review of the study. Thus, FDA is not persuaded that these types of changes in the regulation are now warranted. The agency emphasizes, however, that it applies the regulation with judgment, not as a check-list. A scientifically acceptable study is not rejected because of minor technical deficiencies if it is apparent that the study is basically sound. Moreover, the regulation permits applicants to seek a waiver of individual requirements with respect to investigations.

125. Several comments were concerned that the agency's reordering of the types of controls that may be applied in a study was intended to establish a preferential order for the types of studies supporting an application. One comment said that because the proposal listed placebo concurrent control first, it implied that such a study is preferred over, for instance, a study using a historical control that was listed last. Several comments objected to this implied preferential order of studies because it would encourage researchers to adopt one type of study over another based on FDA's views, instead of considerations about the treatment of patients. These comments recommended that the final rule should clearly state that no study method is preferred over another.

Although the final rule lists the types of controlled studies in a different order than in the current regulation, the reordering does not mean that FDA considers one type of control to be necessarily preferred over another. The reordering is intended simply to reflect FDA's experience that some types of studies (e.g., placebo-controlled studies) are often easier to interpret than other kinds of studies (e.g., those using a historical control). Thus, FDA has listed the types of controls in descending order roughly in accordance with the ease of interpretation. (For this reason, the dose-comparison concurrent control has been moved to second on this list, rather than fourth.) FDA recognizes, however, that ethical and practical considerations will play a central role in the type of study selected, a decision that will ordinarily depend upon the type and seriousness of the disease being treated, availability of alternative therapies, and the nature of the drug and the patient population. In each case, applicants must choose the particular type of study they will use based on ethical, scientific, and practical reasons. So long as these judgments are justifiable, and the studies are properly designed, the approvability of an application will not be affected. Thus, the regulation lists five different kinds of controls that are acceptable; it does not state a perference for one kind over another.

126. Two comments suggested that the final rule distinguished between therapeutic and diagnostic new drugs in determining the appropriate features of an adequate and well-controlled study of the drug. For example, according to thes comments, a placebo concurrent control study would neve be indicated for diagnostic products, such as radiopharmaceutical and contrast media that are intended to have no physiological or therapeutic effect. One comment suggested that current regulations be modified to recognized more clearly this distinction.

FDA agrees that there are good reasons for using different study designs in particular situations, and the agency believes that the regulation is sufficiently flexible to accommodate the needs of applicants in this respect. As a matter of past practice, the agency has approved products whose safety and effectiveness were established using each of the controls listed in the regulation. However, because of the many situations involved, the agency believes it is neither necessary nor feasible to describe them specifically in the regulation.

127. One comment urged that the standard for obtaining a waiver from the adequate and well-controlled study criteria should be changed to require a statement of why a particular criterion need not be applied to the particular clinical investigation "in view of other factors," instead of a statement of why the criteria are not "reasonably applicable."

FDA disagrees with the comment and has retained the current wording in the final rule. The act states that adequate and well-controlled studies are needed to demonstrate the effectiveness of drug products. The agency's regulation describing the characteristics of adequate and well-controlled studies, which is modified only slightly in this final rule, has served satisfactorily as a basis for approvals over time and, as discussed above, contains the essential elements of such studies. Thus FDA concludes that a narrow waiver provision that requires well-justified bases for an exemption should be retained.

128. FDA has, on its own initiative, made the following changes in the final rule describing adequate and well-controlled studies.

First, FDA proposed to delete the current requirement that the method of analysis be included in the plan or protocol of a study. The rationale for this proposed change was that, although having the method of analysis in the plan or protocol has been listed as a characteristic of an adequate and well-controlled study, many protocols, especially those developed years ago, lacked this characteristic. While FDA does not believe the omission of this information means a study is not well-controlled, there is no doubt that the development of a tentative plan for analysis: (a) Minimizes the potential for analyst bias; and (b) helps focus attention on whether it is practical to collect the data and whether variables to be obtained are analyzable. Accordingly, the final rule encourages inclusion of such a plan for analysis in the protocol but permits, as an alternative, the study report to include a description of how the analysis was selected.

Second, at a number of points the regulation has been modified to address potential problems associated with multiple or interim data analyses. These do not render a study less than well-controlled, but they must be described and reflected in the analysis.

Finally, FDA has modified the description of the active treatment concurrent control. This is because a demonstration of effectiveness by means of showing similarity of the test drug to an active control is an indirect demonstration of effectiveness (the active control treatment serving as an intermediary in a comparison between the test drug and placebo). Under this study design, similarity of test drug and active control drug can mean either that both drugs were effective or that neither was effective. Thus, the agency has added a requirement that the analysis of the study provide an explanation of why the active control drug should be considered to have been effective in the completed study, for example, by reference to results in previous placebo-controlled studies of the active control drug.

Withdrawal of Approval of an Application (§ 314.150)

129. One comment suggested that the final rule provide that if FDA found a study to be adequate and well-controlled when it approved the application, that conclusion should remain unchanged even if FDA later adopted new standards under which the study would not be considered adequate and well-controlled. The conclusion would thus preclude withdrawal of the drug's approval upon the basis of new information and an FDA determination that there is a lack of substantial evidence from adequate and well-controlled investigations that the drug is effective.

FDA disagrees with the comment. The factors leading to a determination of what is an adequate and well-controlled study, which is the basis for determining drug efficacy, may, as the comment recognizes, evolve. FDA has an obligation to judge a drug's effectiveness by contemporary scientific standards. If those standards change to the extent that it is questionable whether a drug can be regarded as having been shown to be effective, FDA may under the act appropriately review the drug's status.

Adulteration and Misbranding of an Approved Drug (§ 314.170)

130. One comment supported FDA's proposed clarification of the relationship between the new drug and antibiotic approval provisions of the act and the adulteration and misbranding provisions. In contrast, several comments urged that this section be deleted, believing that the only lawful procedure for dealing with adulterated or misbranded approved new drugs is by withdrawal of approval of the application.

FDA has retained this provision in the final rule. The comments that opposed it submitted no persuasive argument that FDA is incorrect in its position that the new drug provisions do not insulate approved drugs and antibiotics from the general adulteration and misbranding provisions of the act. As FDA has previously noted, the statutory scheme contemplates FDA's application of the adulteration and misbranding standards to all drugs, irrespective of whether those drugs have been subject to the premarket approval requirements of the act.

Hearing Procedures for New Drugs (Subpart D)

131. FDA agrees with one comment that objected to a change in the hearing procedure to remove the requirement that the Director of the Center for Drugs and Biologics serve a proposed order to, and provide for a response from, a person who submits required data or information and requests a hearing following a general or specific notice of an opportunity for hearing. The final rule retains the current requirement.

Administrative Procedures For Antibiotics (Subpart E)

132. One comment suggested that the procedure for issuing antibiotic regulations should be revised to make it as consistent as possible with the approval procedure for new drugs and to expedite the petitioning, rulemaking, and hearing process required under section 507(f) of the act *(21 U.S.C. 357*(f)) when FDA refuses to approve a new antibiotic.

FDA believes it has already taken adequate steps to conform the administrative procedures that apply to refusals to approve (or withdrawals of approval of) antibiotics and new drugs. The procedures for withdrawing approval of an NDA apply to approved antibiotics (which are now all exempt from certification requirements under § 433.1 (21 CFR 433.1)). A full discussion of the regulatory process applicable to antibiotic drugs maybe found in the final rule exempting antibiotic drugs from certification *(47 FR 39155;* September 7, 1982) and in the proposed rule preceding that action *(47 FR 19954;* May 7, 1982). Because the potential exists for a manufacturer to apply voluntarily for batch certification of an antibiotic drug or for FDA to revoke the exemption from batch certification requirements granted to a drug, this final rule retains those provisions necessary for certification of an antibiotic drug, if necessary. In the case of refusals to approve an antibiotic application, while the statutorily based regulatory scheme for the publication of monographs has been retained, the procedures preceding the refusal to approve are, as a practical matter, the same as those employed in a refusal to approve a nonantibiotic application.

Miscellaneous Provisions

133. *Imports § 314.410(a).* Although several comments supported the agency's proposal to permit an individual to bring into the United States a reasonable quantity of an unapproved drug product that is intended only for personal use, several comments argued that the proposal was illegal and would expand illegal trade in unapproved drugs in this country. These comments were especially concerned about what they believed would constitute FDA's sanctioning of the commercialization of drugs generally regarded by the medical community as being useless. One comment suggested that legislation would be needed to make this change. Another comment suggested that FDA would find it difficult to monitor and regulate this exemption.

The proposal was intended to state the agency's discretionary enforcement policy that it can apply to accommodate the health needs of individuals entering the United States with personal supplies of unapproved drugs. Upon reevaluation, however, FDA finds that policy related to enforcement discretion is better stated in a compliance policy guide. Accordingly, this provision has been deleted from the final rule.

134. *Exports (§ 314.410(b)).* One comment suggested that FDA seek legislative changes to permit the export of new drug substances and products under the same conditions that apply to the export of antibiotics. Others suggested that, even without legislation, FDA could permit the export of unapproved drug products and of bulk substances which are not covered by an approved application for a drug product. Another comment stated that the current restrictions on exports of unapproved new drugs discourage the manufacture of human drugs in the United States before approval for marketing in this country. According to this comment, because U.S. approval often occurs after foreign approval, these restrictions require that foreign facilities be built to supply foreign markets, resulting in a significant loss of domestic jobs.

Although FDA recognizes the practical impact of current restrictions on the export of unapproved new drug products and bulk new drug substances, FDA believes that it is obligated to reject the comments recommending changes in the final rule. The definition of "interstate commerce" in section 201(b)(1) of the act *(21 U.S.C. 321*(b)(1)), when read together with the prohibitions on interstate shipment of unapproved new drugs in sections 301(d) and 505(a) *(21 U.S.C. 331*(d) and 355(a)), prohibit the exportation of an unapproved new drug. Section 801(d) of the act *(21 U.S.C. 381*(d)), which grants an exemption from the adulteration and misbranding sections of the act for export purposes, does not grant a similar exemption from the new drug provisions. Therefore, FDA has interpreted the act as reflecting a Congressional intent that unapproved new drugs not be exported, though it has, in the past, supported modification of the statutory export provisions (see, for example, proposed section 135 of the Drug Regulation Reform Act of 1978).

135. One comment, believing that the exporter of a drug substance might have no relationship with the domestic marketer of an approved product, expressed concern that the proposal to broaden the rules on exporting a drug substance could result in exports of a drug substance unsuitable for use in an approved product. Thus, the comment recommended that that provision be limited to manufacturers of approved drug products or exporters of bulk substances that have filed drug master files with the agency covering the manufacturing operations and specifications for the drug substance. Another comment suggested that this proposal was inconsistent with § 201.122(c) of FDA's labeling regulations.

Because FDA believes the first comment misunderstood this provision, the agency has revised the final rule to clarify it. The statutory scheme provides that a new drug substance can be exported only if it is the subject of an approved application. Through this new regulation, FDA is interpreting the application approval to extend to a supplier of a new drug substance under that approved application. Currently, only the applicant who holds the approved application may export the drug substance that is used in the manufacture of the approved drug product, whether or not the applicant is itself the manufacturer of the drug substance. The final rule extends to the person (and only to that person or persons) who is identified in an approved application as the source of the drug substance, but is not itself the applicant, permission to export the drug substance, if the substance meets the specifications in the approved application. Thus, FDA will consider the supplier to be covered by the application both when it ships the drug substance to the applicant and when it exports it. Domestic shipment to a party not the applicant, however, will not be permitted.

FDA does not believe this regulatory change will present the safety concerns raised by the comment because FDA will have already conducted a thorough examination of the drug substance, either in the original application or in a supplement.

However, because the drug substance manufacturer's opportunity to export the substance is dependent upon its inclusion in an approved application, it is also dependent on the applicant's continued inclusion as a supplier in its application. The applicant is always free to supplement its application to change suppliers. Such action, under the final rule, would also have the effect of terminating the former supplier's export rights. Moreover, because no approval has been

provided to suppliers under the act, FDA does not view the hearing requirement of section 505 of the act to apply to a drug substance supplier who is so terminated by an applicant.

In response to the second comment, FDA does not agree that the filing of a drug master file should be sufficient to acquire a right to export a drug substance. FDA does not review a drug master file except in the context of the agency's review of an application or supplement that references it. Thus, the submission of a drug master file does not now result in any agency action. FDA does not intend to revise this practice by reviewing drug master files independently. Resource constraints on FDA and the lack of a drug product and proper labeling by which to measure the suitability of the drug substance for any purpose warrant maintaining the current practice. Finally, FDA has revised § 201.122(a) to clarify that a drug substance may be exported under the labeling exemption provided by that section, if it is covered by an approved application.

136. *Drug master files (§ 314.420).* Several comments objected to the proposed requirement that a drug master file holder notify each person authorized to refer to information if the holder adds, changes, or deletes the information. Some comments stated that drug master file holders generally give umbrella authorization to others for use of their master files and that the regulations are unclear about how specific a notification must be made to persons authorized to reference information when the holder adds, changes, or deletes information in the file. Thus, according to these comments, the provision is unnecessarily burdensome and could result in the unwarranted disclosure of trade secrets.

FDA has retained the provision in the final rule. FDA believes that applications that depend upon information in drug master files may quickly become outdated if the drug master file holder does not notify the persons authorized to reference the file about changes in the information in it. Because FDA reviews the contents of a drug master file only in the context of its review of an application or a supplement to an application, a change in important information in a drug master file that may affect the safety and effectiveness of a drug product is not likely to be reviewed unless the owner of the master file notifies the applicant who, in turn, submits a supplement to incorporate the change in its approved application. Recognizing that one of the primary functions of the drug master file system is to maintain the confidentiality of trade secret information, FDA agrees that a file holder's notification about changes in the file does not have to be so specific that the confidentiality of information in the file is compromised.

137. One comment asked whether the requirement that the drug master file contain a complete list of persons currently authorized to reference it can be met by individual letters whenever a person is authorized or an authorization is revoked.

FDA notes that some drug master files are voluminous and subject to substantial amendments over time. Thus, it may be impossible to determine from individual letters submitted at different times the person who is currently authorized to reference a file. For that reason, FDA believes that a single list of persons currently authorized to reference the file should be maintained.

138. One comment urged that the changes in the regulation on drug master files should apply only to information added to the master file after the date of publication of the final rule. Another comment urged that the changes apply only to applications submitted after the effective date which incorporate a drug master file reference.

FDA believes that a uniform effective date for changes in the regulation on drug master files is necessary. Applying the regulations only to information added to a file after publication of the final rule, or applications submitted after the effective date of the final rule, would lead to continual confusion about what part of the file is subject to the rule.

139. *Designated journals (§ 310.9).* One comment objected to FDA removing its list of designated journals from the regulations. The comment urged FDA to retain a list of journals that are available to it and waive requirements for submission or reprints and summaries of reports in those journals.

As discussed elsewhere in this preamble, FDA does not believe it to be a wise expenditure of its resources to retrieve copies of referenced journals from its library, given the minimal burden on applicants to submit relevant copies. FDA notes that the change is more likely to expedite rather than delay review of applications. In addition to removing § 310.9, FDA also is deleting the references to § 310.9 that appear in 21 CFR 510.3(1) and 510.95.

140. *Public information (§ 314.430).* One comment contended that FDA's classification of what constitutes confidential safety and effectiveness data in an application is overbroad and that, instead, the agency should require the applicant to index confidential records within its application in a manner similar to the procedure in § 20.53 (21 CFR 20.53) of FDA's public information regultions. If a person requests a copy of a record the applicant considers confiden-

tial, the applicant's reasons for considering it confidential could be forwarded to the requestor, who may then ask the agency to determine whether the record is disclosable.

FDA does not agree with this comment. An applicant is required to itemize and index its records under § 20.53 only in a legal action contesting an FDA denial of a request for records because they are exempt from public disclosure as a trade secret or confidential commercial or financial data and information. The agency believes that the comment's suggestion that this procedure be established absent litigation, and before FDA makes an initial determination about the status of a document, would impose a significant burden on applicants to index large numbers of records whose confidential status will never be disputed. It would also add to FDA's already heavy workload in responding to freedom of information requests by requiring the agency to provide the requestor with a preliminary response detailing the applicant's reasons for considering a record nondisclosable.

141. In § 314.430(f) of the proposal, FDA proposed to modify § 314.14(f) of the current regulations in identifying the situations in which safety and effectiveness data and information are available for public disclosure. Consideration of that proposal, as it relates to disclosure rules for drugs submitted under section 505(b) of the act, was rendered moot, however, by section 104 of the Drug Price Competition and Patent Term Restoration Act of 1984, enacted on September 24, 1984, because the new law itself provides when data and information in such submissions are publicly disclosable. Accordingly, FDA has conformed this final rule (§ 314.430(f)) to be consistent with section 104 of the new law.

In doing so, FDA calls attention to one specific point. Section 314.14(f)(5) of the current regulations provides that safety and effectiveness data and information are publicly disclosable when a final determination has been made that the drug may be approved without the submission of such data and information. In the past, "final determination" (for drugs approved under section 505) was interpreted to require publication of a final Federal Register notice under the Drug Efficacy Study Implementation (DESI) program. Under the new law, however, this provision means such data and information are publicly disclosable as soon as an abbreviated application under section 505(j) of the act for the product can be made effective, and that point in time will be identifiable through the list pubished monthly in accordance with section 505(j)(6) of the act.

For applications submitted under sections 505(j), 506, and 507 of the act, FDA has added § 314.430(f)(6) which states that safety and effectiveness data and information will be publicly disclosable when FDA sends an approval letter to the applicant. To prevent redundancy, FDA had deleted proposed § 314.430(e)(1) for the final rule.

142. *Waivers (§ 314.90).* One comment suggested that FDA not issue a final provision permitting it to waive requirements for the submission of information in an application. This comment feared that the waiver provision would permit applicants to market new products without having to submit adequate clinical information and other data about its safety and efficacy.

FDA believes this comment misunderstands the scope of the waiver provision, which is intended to give applicants the flexibility to seek alternative ways of complying with the regulatory requirements for drug approval. FDA is unable, and does not view the provision as authorizing it, to waive statutory requirements.

143. *Other changes.* On its own initiative, FDA has revised the final rule to retain current requirements, described below, that were inadvertently omitted from the proposal in the sections concerning contents of an application (§ 314.50), refusal to file an application (§ 314.101(d)), refusal to approve an application (§ 314.125), and/or withdrawal of approval of an application (§ 314.150).

First, the final rule provides that an application must contain reports of all investigations of the drug sponsored by the applicant, and all other information pertinent to an evaluation of the application that is received or otherwise obtained by the applicant from any source. To correspond to this requirement, the final rule also provides that FDA may refuse to approve (or withdraw approval of) an application if it does not explain the omission of a report of any investigation of a drug sponsored by the applicant, or the omission of other information pertinent to an evaluation of the application that is received or otherwise obtained by the applicant from any source. Although the proposal contained a requirement that the applicant submit all information pertinent to the evaluation of the application, it did not clearly require an applicant to submit reports of all the studies it sponsors nor did it provide for FDA to refuse to file or approve, or to withdraw approval of, an application that omits required reports or an explanation of the omission (all of which are current requirements).

Second, the final rule underscores the importance of conducting clinical investigations involving human subjects in compliance with the institutional review board regulations in Part 56 and the informed consent regulations in Part 50. In this regard, the final rule provides that the application must contain a statement for each clinical study subject to those

regulations that the study was conducted in compliance with them. The agency may refuse to file an application, under the final rule, if the requisite statement is not provided. Also under the final rule, FDA may refuse to approve (or withdraw approval of) an application if the noncompliance results in the rights or safety of human subjects not being adequately protected. These requirements were added to the current regulations in the Federal Register of January 27, 1981 *(46 FR 8942, 8954),* but they were inadvertently omitted from the proposal. The language used in the final rule constitutes a minor change from current regulations to clarify that FDA would not refuse to approve (or withdraw approval of) an application because of minor technical deviations from these regulations not affecting the rights of safety of human subjects. For purposes of consistency, FDA is also revising § 312.1(d)(11) to conform the provision respecting termination of an IND to the language used in this final rule.

Similarly, the final rule, like the current regulations and the proposal, underscores the importance of conducting nonclinical laboratory studies in compliance with the good laboratory practice regulations in Part 58. The language in the final rule has been revised to state that for each nonclinical study not conducted in compliance with these regulations, the application must contain a brief statement of the reason for the noncompliance (rather than a detailed description of all differences between the practices used in the study and those in the regulations). The language used in the final rule reflects advice that FDA has been providing to applicants with respect to interpretation of the current regulatory provision. The section on refusing to file an application has been conformed accordingly. For purposes of consistency, FDA is also revising the following sections of Title 21 of the Code of Federal Regulations with respect to applications submitted to FDA for research or marketing permits where the submission includes the results of nonclinical laboratory studies subject to Part 58, in order to conform those sections to the language used in this final rule: § § 71.1, 71.6, 170.35, 171.1, 171.6, 180.1, 312.1, 330.10, 511.1, 514.1, 514.8, 514.15, 514.110, 570.35, 571.1, 571.6, 602.1, 812.27, 1003.31, 1010.4, and 1010.5.

Finally, also with respect to compliance with Part 58, the final rule, like the proposal, provides that FDA may refuse to approve an application if the nature of the noncompliance does not support the validity of the study. This language is intended to clarify that FDA would not refuse to approve an application because of minor technical deviations from these regulations. The final rule also contains a parallel provision in the section on withdrawal of approval, which was inadvertently omitted from the proposal. For purposes of consistency, FDA is also revising § § 312.1(d)(12), 514.111(a)(11), and 514.115(b)(4) to conform these provisions governing investigational new drug and new animal drug applications to the language used in this final rule.

List of Subjects

21 CFR Part 71

Administrative practice and procedure, Color additive certification, Color additive petitions, Color additives, Cosmetics, Drugs.

21 CFR Part 170

Administrative practice and procedure, Definitions, Food additives, Food additive safety.

21 CFR Part 171

Administrative practice and procedure, Food additive petitions, Food additives.

21 CFR Part 180

Food additives, Interim listed food additives.

21 CFR Part 201

Drugs, Labeling.

21 CFR Part 310

Administrative practice and procedure, Drugs, Medical devices, Reporting requirements.

21 CFR Part 312

Drugs, Medical research.

21 CFR Part 314

Administrative practice and procedure, Drugs.

21 CFR Part 330

Over-the-counter drugs.

21 CFR Part 430

Administrative practice and procedure, Antibiotics.

21 CFR Part 431

Administrative practice and procedure, Antibiotics.

21 CFR Part 433

Antibiotics, Labeling.

21 CFR Part 510

Administrative practice and procedure, Animal drugs, Labeling, Reporting requirements.

21 CFR Part 511

Animal drugs, Medical research.

21 CFR Part 514

Administrative practice and procedure, Animal drugs.

21 CFR Part 570

Animal feeds, Animal foods, Food additives.

21 CFR Part 571

Administrative practice and procedure, Animal feeds, Animal foods, Food additives.

21 CFR Part 601

Biologics.

21 CFR Part 812

Health records, Investigational device exemptions, Medical devices, Medical device research, Reporting requiements.

21 CFR Part 1003

Administrative practice and procedure, Defects, Electronic products, Noncompliance, Radiation protection.

21 CFR Part 1010

Administrative practice and procedure, Electronic products, Exemptions, Exports, Radiation protection, Standards, Variances.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 409, 501, 502, 503, 505, 506, 507, 512-516, 520, 701, 706, 52 Stat. 1049-1053 as amended, 1055-1056 as amended, 55 Stat. 851, 59 Stat. 463 as amended, 72 Stat. 1785-1788 as amended, 74 Stat. 399-407 as amended, 82 Stat. 343-351, 90 Stat. 540-560 *(21 U.S.C. 348, 351, 352, 353, 355, 356, 357, 360b-360f, 371, 376))* and the Public Health Service Act (secs. 215, 301, 351, 354-360f, 58 Stat. 690, 702 as amended, 82 Stat. 1173-1186 as amended *(42 U.S.C. 216, 241, 262, 263b-263n))* and under 21 CFR 5.11, Parts 71, 170, 171, 180, 201, 310, 312, 314, 430, 431, 433, 510, 511, 514, 570, 601, 812, 1003, and 1010 are amended as follows:

PART 71 -- COLOR ADDITIVE PETITIONS

1. Part 71 is amended:

a. In § 71.1 by revising paragraph (g), to read as follows:

§ 71.1 Petitions.

* * * * *

(g) If nonclinical laboratory studies are involved, petitions filed with the Commissioner under section 706(b) of the act shall include with respect to each nonclinical study contained in the petition, either a statement that the study was conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

* * * * *

b. In § 71.6 by revising the third sentence of paragraph (b), to read as follows:

§ 71.6 Extension of time for studying petitions; substantive amendments; withdrawal of petitions without prejudice.

* * * * *

(b) * * * If nonclinical laboratory studies are involved, additional information and data submitted in support of filed petitions shall include, with respect to each nonclinical laboratory study contained in the petition, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance. * * *

* * * * *

PART 170 -- FOOD ADDITIVES

2. Part 170 is amended in § 170.35 by revising paragraph (c)(1)(vi), to read as follows:

§ 170.35 Affirmation of generally recognized as safe (GRAS) status.

* * * * *

(c) * * *

(1) * * *

(vi) If nonclinical laboratory studies are involved, additional information and data submitted in support of filed petitions shall include, with respect to each nonclinical study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

* * * * *

PART 171 -- FOOD ADDITIVE PETITIONS

3. Part 171 is amended:

a. In § 171.1 by revising paragraph (k), to read as follows:

§ 171.1 Petitions.

* * * * *

(k) If nonclinical laboratory studies are involved, petitions filed with the Commissioner under section 409(b) of the act shall include, with respect to each nonclinical study contained in the petition, either a statement that the study has been, or will be, conducted in compliance with the good laboratory practice regulations as set forth in Part 58 of this chapter, or if any such study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

* * * * *

b. By revising § 171.6, to read as follows:

§ 171.6 Amendment of petition.

After a petition has been filed, the petitioner may submit additional information or data in support thereof. In such cases, if the Commissioner determines that the additional information or data amount to a substantive amendment, the petition as amended will be given a new filing date, and the time limitation will begin to run anew. Where the substantive amendment proposes a substantial change to any petition that may affect the quality of the human environment, the petitioner is required to submit an environmental analysis report pursuant to § 25.1 of this chapter. If nonclinical laboratory studies are involved, additional information and data submitted in support of filed petitions shall include, with respect to each nonclinical study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

PART 180 -- FOOD ADDITIVES PERMITTED IN FOOD ON AN INTERIM BASIS OR IN CONTACT WITH FOOD PENDING ADDITIONAL STUDY

4. Part 180 is amended in § 180.1 by revising paragraph (c)(4), to read as follows:

§ 180.1 General.

* * * * *

(c) * * *

(4) If nonclinical laboratory studies are involved, studies filed with the Commissioner shall include, with respect to each study, either a statement that the study has been or will be conducted in compliance with the good laboratory practice regulations as set forth in Part 58 of this chapter, or, if any such study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

* * * * *

PART 201 -- LABELING

5. Part 201 is amended in § 201.122 by revising paragraph (a), to read as follows:

§ 201.122 Drugs for processing, repacking, or manufacturing.

* * * * *

(a) An approved new drug application or new animal drug application covers the production and delivery of the drug substance to the application holder by persons named in the application, and, for a new drug substance, the export of it by such persons under § 314.410 of this chapter; or

* * * * *

PART 310 -- NEW DRUGS

6. Part 310 is amended:

§ 310.3 [Amended]

a. In § 310.3 *Definitions and interpretations* by removing and reserving paragraph (m).

§ 310.9 [Removed]

b. By removing § 310.9 *Designated journals.*

§ 310.300 [Removed]

c. By removing § 310.300 *Records and reports concerning experience on drugs for which an approval is in effect.*

§ 310.301 [Removed]

d. By removing § 310.301 *Reporting of adverse drug experiences.*

§ 310.302 [Removed]

e. By removing § 310.302 *Records and reports on new drugs and antibiotics for use by man for which applications or certification forms 5 and 6 became effective or were approved prior to June 20, 1963.*

PART 312 -- NEW DRUGS FOR INVESTIGATIONAL USE

7. Part 312 is amended:

a. In § 312.1 by revising item 16 in Form FD-1571 in paragraph (a)(2) and by revising paragraph (d) (11) and (12), to read as follows:

§ 312.1 Conditions for exemption of new drugs for investigational use.

(a) * * *

(2) * * *

Form FD-1571 * * *

16. A statement that all nonclinical laboratory studies have been, or will be, conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or, if such studies have not been conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

* * * * *

(d) * * *

(11) Any clinical investigation involving human subjects, subject to the institutional review board regulations in Part 56 of this chapter or informed consent regulations in Part 50 of this chapter, is not being conducted in compliance with those regulations such that the rights or safety of human subjects are not adequately protected; or

(12) Any nonclinical laboratory study that is described in the notice of claimed investigational exemption and that is essential to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling, was not conducted in compliance with the good laboratory practice regulations as set forth in Part 58 of

this chapter and no reason for the noncompliance is provided or, if it is, the differences between the practices used in conducting the study and the good laboratory practice regulations do not support the validity of the study; or

* * * * *

b. In § 312.20 by revising paragraph (c), to read as follows:

§ 312.20 Clinical data generated outside the United States and not subject to a "Notice of Claimed Investigational Exemption for a New Drug."

* * * * *

(c) Data from studies performed outside the United States and conducted in accordance with the requirements of this section may be utilized without duplication of the studies in the United States, as appropriate.

* * * * *

8. By revising Part 314 to read as follows:

PART 314 -- APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG

Subpart A -- General Provisions

Sec.

314.1 Scope of this part.

314.2 Purpose.

314.3 Definitions.

Subpart B -- Applications

314.50 Content and format of an application.

314.55 Abbreviated application.

314.56 Drug products for which abbreviated applications are suitable.

314.60 Amendments to an unapproved application.

314.65 Withdrawal by the applicant of an unapproved application.

314.70 Supplements and other changes to an approved application.

314.71 Procedures for submission of a supplement to an approved application.

314.72 Change in ownership of an application.

314.80 Postmarketing reporting of adverse drug experiences.

Authority: Secs. 409, 501, 502, 503, 505, 506, 507, 512-516, 520, 701, 706, 52 Stat. 1049-1053 as amended, 1055-1056 as amended, 55 Stat. 851, 59 stat. 463 as amended, 72 Stat. 1785-1788 as amended, 74 Stat. 399-407 as amended, 82 Stat. 343-351, 90 Stat. 540-560 *(21 U.S.C. 351, 352, 353, 355, 356, 357, 360b-360f, 371, 376);* sec. 215, 301, 351, 354-360F, 58 Stat. 690, 702 as amended, 82 Stat. 1173-1186 as amended *(42 U.S.C. 216, 241, 262, 263b-263n).*

Subpart A -- General Provisions

§ 314.1 Scope of this part.

(a) This part sets forth procedures and requirements for the submission to, and the review by, the Food and Drug Administration fo applications and abbreviated applications, as well as amendments, supplements, and postmarketing reports to them, by persons seeking or holding approval from FDA of the following:

(1) An application under section 505 of the Federal Food, Drug, and Cosmetic Act to market a new drug.

(2) An application under section 507 of the Federal Food, Drug, and Cosmetic Act to market an antibiotic drug.

(b) This part does not apply to drug products subject to licensing by FDA under the Public Health Service Act (58 Stat. 632 as amended *(42 U.S.C. 201* et seq.)) and Subchapter F of Chapter I of Title 21 of the Code of Federal Regulations.

(c) References in this part to regulations in the Code of Federal Regulations are to Chapter I of Title 21, unless otherwise noted.

§ 314.2 Purpose.

The purpose of this part is to establish an efficient and thorough drug review process in order to: (a) Facilitate the approval of drugs shown to be safe and effective; and (b) ensure the disapproval of drugs not shown to be safe and effective. These regulations are also intended to establish and effective system for FDA's surveillance of marketed drugs. These regulations shall be construed in light of these objectives.

§ 314.3 Definitions.

(a) The definitions and interpretations contained in section 201 of the act apply to those terms when used in this part.

(b) The following definitions of terms apply to this part:

"Act" means the Federal Food, Drug, and Cosmetic Act (sections 201-901, 52 Stat. 1040 et seq., as amended *(21 U.S.C. 301-392)).*

"Applicant" means any person who submits an application or abbreviated application or an amendment or supplement to them under this part to obtain Food and Drug Administration approval of a new drug or an antibiotic drug and any person who owns an approved application.

"Application" means both the application described under § 314.50 and the abbreviated application under § 314.55, including all amendments and supplements.

"Approvable letter" means a written communication to an applicant from FDA stating that the agency will approve the application if specific additional information or material is submitted or specific conditions are met. An approvable letter does not constitute approval of any part of an application and does not permit marketing of the drug that is the subject of the application.

"Approval letter" means a written communication to an applicant from FDA approving an application. An approval letter permits marketing of the drug product that is the subject of the application.

"Drug product" means a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.

"Drug substance" means an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure of any function of the human body, but does not include intermediates used in the synthesis of such ingredient.

"FDA" means the Food and Drug Administration.

"Not approvable letter" means a written communication to an applicant from FDA stating that the agency does not consider the application approvable because one or more deficiencies in the application preclude the agency from approving it.

Subpart B -- Applications

§ 314.50 Content and format of an application.

Applications, including abbreviated applications, and supplements to approved applications are required to be submitted in the form and contain the information, as appropriate for the particular submission, required under this section. Two copies of the application are required, an archival copy and a review copy. An application for a new chemical entity will generally contain an application form, an index, a summary, five or six technical sections, case report tabulations of patient data, case report forms, drug samples, and labeling. Other applications will generally contain only some of those items, and information will be limited to that needed to support the particular submission. These include an application for a duplicate of a marketed drug product (such as a "paper NDA," which relies primarily on published literature to provide substantial evidence of effectiveness and adequate scientific evidence of safety for the claimed indications), an abbreviated application, an amendment, and a supplement. The application is required to contain reports of all investigations of the drug product sponsored by the applicant, and all other information about the drug pertinent to an evaluation of the application that is received or otherwise obtained by the applicant from any source. The Food and Drug Administration will maintain guidelines on the format and content of applications to assist applicants in their preparation.

(a) *Application form.* The applicant shall submit a completed and signed application form that contains the following:

(1) The name and address of the applicant; the date of the application; the application number if previously issued (for example, if the application is a resubmission, an amendment, or a supplement); the name of the drug product, including its established, proprietary, code, and chemical names; the dosage form and strength; the route of administration; the identification numbers of all investigational new drug applications that are referenced in the application; the identification numbers of all drug master files and other applications under this part that are referenced in the application; and the drug product's proposed indications for use.

(2) A statement whether the submission is an original submission, a resubmission, an abbreviated application under § 314.55, or a supplement to an application under § 314.70.

(3) A statement whether the applicant proposes to market the drug product as a prescription or an over-the-counter product.

(4) A check-list identifying what enclosures required under this section the applicant is submitting.

(5) The applicant, or the applicant's attorney, agent, or other authorized official shall sign the application. If the person signing the application does not reside or have a place of business within the United States, the application is required to contain the name and address of, and be countersigned by, an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

(b) *Index.* The archival copy of the application is required to contain a comprehensive index by volume number and page number to the summary under paragraph (c) of this section, the technical sections under paragraph (d) of this section, and the supporting information under paragraph (f) of this section.

(c) *Summary.* (1) An application is required to contain a summary of the application in enough detail that the reader may gain a good general understanding of the data and information in the application, including an understanding of the quantitative aspects of the data. The summary is not required for abbreviated applications under § 314.55 and supplements under § 314.70. Resubmissions of an application should contain an updated summary, as appropriate. The summary should discuss all aspects of the application, and synthesize the information into a well-structured and unified document. The summary should be written at approximately the level of detail required for publication in, and meet the editorial standards generally applied by, refereed scientific and medical journals. In addition to the agency personnel reviewing the summary in the context of their review of the application, FDA may furnish the summary to FDA advisory committee members and agency officials whose duties require an understanding of the application. To the extent possible, data in the summary should be presented in tabular and graphic forms. FDA has prepared a guideline under § 10.90(b) that provides information about how to prepare a summary. The summary required under this paragraph may be used by FDA or the applicant to prepare the Summary Basis of Approval document for public disclosure (under § 314.430(e)(2)(ii)) when the application is approved.

(2) The summary is required to contain the following information:

(i) The proposed text of the labeling for the drug, with annotations to the information in the summary and technical sections of the application that support the inclusion of each statement in the labeling, and, if the application is for a prescription drug, statements describing the reasons for omitting a section or subsection of the labeling format in § 201.57.

(ii) A statement identifying the pharmacologic class of the drug and a discussion of the scientific rationale for the drug, its intended use, and the potential clinical benefits of the drug product.

(iii) A brief description of the marketing history, if any, of the drug outside the United States, including a list of the countries in which the drug has been marketed, a list of any countries in which the drug has been withdrawn from marketing for any reason related to safety or effectiveness, and a list of countries in which applications for marketing are pending. The description is required to describe both marketing by the applicant and, if known, the marketing history of other persons.

(iv) A summary of the chemistry, manufacturing, and controls section of the application.

(v) A summary of the nonclinical pharmacology and toxicology section of the application.

(vi) A summary of the human pharmacokinetics and bioavailability section of the application.

(vii) A summary of the microbiology section of the application (for anti-infective drugs only).

(viii) A summary of the clinical data section of the application, including the results of statistical analyses of the clinical trials.

(ix) A concluding discussion that presents the benefit and risk considerations related to the drug, including a discussion of any proposed additional studies or surveillance the applicant intends to conduct postmarketing.

(d) *Technical sections.* The application is required to contain the technical sections described below. Each technical section is required to contain data and information in sufficient detail to permit the agency to make a knowledgeable judgment about whether to approve the application or whether grounds exist under section 505(d) or 507 of the act to refuse to approve the application. The required technical sections are as follows:

(1) *Chemistry, manufacturing, and controls section.* A section describing the composition, manufacture, and specification of the drug substance and the drug product, including the following:

(i) *Drug substance.* A full description of the drug substance including its physical and chemical characteristics and stability; the name and address of its manufacturer; the method of synthesis (or isolation) and purification of the drug substance; the process controls used during manufacture and packaging; and such specifications and analytical methods as are necessary to assure the identity, strength, quality, and purity of the drug substance and the bioavailability of the drug products made from the substance, including, for example, specifications relating to stability, sterility, particle size, and crystalline form. The application may provide additionally for the use of alternatives to meet any of these requirements, including alternative sources, process controls, methods, and specifications. Reference to the current edition of the U.S. Pharmacopeia and the National Formulary may satisfy relevant requirements in this paragraph.

(ii) *Drug product.* A list of all components used in the manufacture of the drug product (regardless of whether they appear in the drug product); and a statement of the composition of the drug product; a statement of the specifications and analytical methods for each component; the name and address of each manufacturer the drug product; a description of the manufacturing and packaging procedures and in-process controls for the drug product; such specifications and analytical methods as are necessary to assure the identity, strength, quality, purity, and bioavailability of the drug product, including, for example, specifications relating to sterility, dissolution rate, containers and closure systems; and stability data with proposed expiration dating. The application may provide additionally for the use of alternatives to meet any of these requirements, including alternative components, manufacturing and packaging procedures, in-process controls, methods, and specifications. Reference to the current edition of the U.S. Pharmacopeia and the National Formulary may satisfy relevant requirements in this paragraph.

(iii) *Environmental impact analysis report.* An environmental impact analysis report under § 25.1 analyzing the environmental impact of the manufacturing process and the ultimate use of the drug product.

(iv) The applicant may, at its option, submit a complete chemistry, manufacturing, and controls section 90 to 120 days before the anticipated submission of the remainder of the application. FDA will review such early submissions as resources permit.

(2) *Nonclinical pharmacology and toxicology section.* A section describing, with the aid of graphs and tables, the nonclinical laboratory studies with the drug, including the following:

(i) Studies of the pharmacological actions of the drug in relation to its proposed therapeutic indication and studies otherwise define the pharmacologic properties of the drug or are pertinent to possible adverse effects.

(ii) Studies of the toxicological effects of the drug as they relate to the drug's intended clinical uses, including, as appropriate, studies assessing the drug's acute, subacute, and chronic toxicity; carcinogenicity; and studies of toxicities related to the drug's particular mode of administration or conditions of use.

(iii) Studies, as appropriate, of the effects of the drug on reproduction and on the developing fetus.

(iv) Any studies of the absorption, distribution, metabolism, and excretion of the drug in animals.

(v) For each nonclinical laboratory study a statement that it was conducted in compliance with the good laboratory practice regulations in Part 58, or, if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

(3) *Human pharmacokinetics and bioavailability section.* A section describing the human pharmacokinetic data and human bioavailability data, or information supporting a waiver of the submission of in vivo bioavailability data under Subpart B of Part 320, including the following:

(i) A description of each of the bioavailability and pharmacokinetic studies of the drug in humans performed by or on behalf of the applicant that includes a description of the analytical and statistical methods used in each study and a statement with respect to each study that it either was conducted in compliance with the institutional review board regulations in Part 56, or was not subject to the regulations under § 56.104 or § 56.105, and that it was conducted in compliance with the informed consent regulations in Part 50.

(ii) If the application describes in the chemistry, manufacturing, and controls section specifications or analytical methods needed to assure the bioavailability of the drug product or drug substance, or both, a statement in this section of the rationale for establishing the specification or analytical methods, including data and information supporting the rationale.

(iii) A summarizing discussion and analysis of the pharmacokinetics and metabolism of the active ingredients and the bioavailability or bioequivalence, or both, of the drug product.

(4) *Microbiology section.* If the drug is an anti-infective drug, a section describing the microbiology data, including the following:

(i) A description of the biochemical basis of the drug's action on microbial physiology.

(ii) A description of the antimicrobial spectra of the drug, including results of in vitro preclinical studies to demonstrate concentrations of the drug required for effective use.

(iii) A description of any known mechanisms of resistance to the drug, including results of any known epidemiologic studies to demonstrate prevalence of resistance factors.

(iv) A description of clinical microbiology laboratory methods (for example, in vitro sensitivity discs) needed for effective use of the drug.

(5) *Clinical data section.* A section describing the clinical investigations of the drug, including the following:

(i) A description and analysis of each clinical pharmacology study of the drug, including a brief comparison of the results of the human studies with the animal pharmacology and toxicology data.

(ii) A description and analysis of each controlled clinical study pertinent to a proposed use of the drug, including the protocol and a description of the statistical analyses used to evaluate the study. If the study report is an interim analysis, this is to be noted and a projected completion date provided. Controlled clinical studies that have not been analyzed in detail for any reason (e.g., because they have been discontinued or are incomplete) are to be included in this section, including a copy of the protocol and a brief description of the results and status of the study.

(iii) A description of each uncontrolled clinical study, a summary of the results, and a brief statement explaining why the study is classified as uncontrolled.

(iv) A description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from clinical investigations, including controlled and uncontrolled studies of uses of the drug other than those proposed in the application, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers.

(v) An integrated summary of the data demonstrating substantial evidence of effectiveness for the claimed indications. Evidence is also required to support the dosage and administration section of the labeling, including support for the dosage and dose interval recommended, and modifications for specific subgroups (for example, pediatrics, geriatrics, patients with renal failure).

(vi) A summary and updates of safety information, as follows:

(*a*) The applicant shall submit an integrated summary of all available information about the safety of the drug product, including pertinent animal data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions, and other safety considerations, such as data from epidemiological studies of related drugs. A description of any statistical analyses performed in analyzing safety data should also be included, unless already included under paragraph (a)(5)(ii) of this section.

(*b*) The applicant shall, under section 505(i) of the act, update periodically its pending application with new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling. These "safety update reports" are required to include the same kinds of information (from clinical studies, animal studies, and other sources) and are required to be submitted in the same format as the integrated summary in paragraph (d)(5)(vi)(*a*) of this section. In addition, the reports are required to include the case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event (unless this requirement is waived). The applicant shall submit these reports (*1*) 4 months after the initial submission; (*2*) following receipt of an approvable letter; and (*3*) at other times as requested by FDA. Prior to the submission of the first such report, applicants are encouraged to consult with FDA regarding further details on its form and content.

(vii) If the drug has a potential for abuse, a description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling under the Controlled Substances Act. A description of any studies related to overdosage is also required, including information on dialysis, antidotes, or other treatments, if known.

(viii) An integrated summary of the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions stated in the labeling.

(ix) A statement with respect to each clinical study involving human subjects that it either was conducted in compliance with the institutional review board regulations in Part 56, or was not subject to the regulations under § 56.104 or § 56.105, and that it was conducted in compliance with the informed consent regulations in Part 50.

(6) *Statistical section.* A section describing the statistical evaluation of clinical data, including the following:

(i) A copy of the information submitted under paragraph (d)(5)(ii) of this section concerning the description and analyses of each controlled clinical study, and the documentation and supporting statistical analysis used in evaluating the controlled clinical studies.

(ii) A copy of the information submitted under paragraph (d)(5)(vi)(*a*) of this section concerning a summary of information about the safety of the drug product, and the documentation and supporting statistical analyses used in evaluating the safety information.

(e) *Samples and labeling.* (1) Upon request from FDA, the applicant shall submit the samples described below to the places identified in the agency's request. FDA will generally ask applicants to submit samples directly to two or more agency laboratories that will perform all necessary tests on the samples and validate the applicant's analytical methods.

(i) Four representative samples of the following, each sample in sufficient quantity to permit FDA to perform three times each test described in the application to determine whether the drug substance and the drug product meet the specifications given in the application:

(*a*) The drug product proposed for marketing;

(*b*) The drug substance used in the drug product from which the samples of the drug product were taken; and

(*c*) Reference standards and blanks (except that reference standards recognized in an official compendium need not be submitted).

(ii) Samples of the finished market package, if requested by FDA.

(2) The applicant shall submit the following in the archival copy of the application:

(i) Three copies of the analytical methods and related descriptive information contained in the chemistry, manufacturing, and controls section under paragraph (d)(1) of this section for the drug substance and the drug product that are necessary for FDA's laboratories to perform all necessary tests on the samples and to validate the applicant's analytical methods. The related descriptive information includes a description of each sample; the proposed regulatory specifications for the drug; a detailed description of the methods of analysis; supporting data for accuracy, specificity, precision and ruggedness; and complete results of the applicant's tests on each sample.

(ii) Copies of the label and all labeling for the drug product (4 copies of draft labeling or 12 copies of final printed labeling).

(f) *Case report forms and tabulations.* The archival copy of the application is required to contain the following case report tabulations and case report forms:

(1) *Case report tabulations.* The application is required to contain tabulations of the data from each adequate and well-controlled study under § 314.126 (Phase 2 and Phase 3 studies as described in § 312.1(a)(2), Form FDA-1571), tabulations of the data from the earliest clinical pharmacology studies (Phase 1 studies as described in § 312.1(a)(2), Form FDA-1517), and tabulations of the safety data from other clinical studies. Routine submission of other patient data from uncontrolled studies is not required. The tabulations are required to include the data on each patient in each study, except that the applicant may delete those tabulations which the agency agrees, in advance, are not pertinent to a review of the drug's safety or effectiveness. Upon request, FDA will discuss with the applicant in a "pre-NDA" conference those tabulations that may be appropriate for such deletion. Barring unforeseen circumstances, tabulations agreed to be deleted at such a conference will not be requested during the conduct of FDA's review of the application. If such un-

foreseen circumstances do occur, any request for deleted tabulations will be made by the director of the FDA division responsible for reviewing the application, in accordance with paragraph (f)(3) of this section.

(2) *Case report forms.* The application is required to contain copies of individual case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event, whether believed to be drug related or not, including patients receiving reference drugs or placebo. This requirement may be waived by FDA for specific studies if the case report forms are unnecessary for a proper review of the study.

(3) *Additional data.* The applicant shall submit to FDA additional case report forms and tabulations needed to conduct a proper review of the application, as requested by the director of the FDA division responsible for reviewing the application. The applicant's failure to submit information requested by FDA within 30 days after receipt of the request may result in the agency viewing any eventual submission as a major amendment under § 314.60 and extending the review period as necessary. If desired by the applicant, the FDA division director will verify in writing any request for additional data that was made orally.

(4) Applicants are invited to meet with FDA before submitting an application to discuss the presentation and format of supporting information. If the applicant and FDA agree, the applicant may submit tabulations of patient data and case report forms in a form other than hard copy, for example, on microfiche or computer tapes.

(g) *Other.* The following general requirements apply to the submission of information within the summary under paragraph (c) of this section and within the technical sections under paragraph (d) of this section.

(1) The applicant ordinarily is not required to resubmit information previously submitted, but may incorporate the information by reference. A reference to information submitted previously is required to identify the file by name, reference number, volume, and page number in the agency's records where the information can be found. A reference to information submitted to the agency by a person other than the applicant is required to contain a written statement that authorizes the reference and that is signed by the person who submitted the information.

(2) The applicant shall submit an accurate and complete English translation of each part of the application that is not in English. The applicant shall submit a copy of each original literature publication for which an English translation is submitted.

(h) *Format of an original application.* (1) The applicant shall submit a complete archival copy of the application that contains the information required under paragraphs (a) through (f) of this section. FDA will maintain the archival copy during the review of the application to permit individual reviewers to refer to information that is not contained in their particular technical sections of the application, to give other agency personnel access to the application for official business, and to maintain in one place a complete copy of the application. An applicant may submit on microfiche the portions of the archival copy of the application described in paragraphs (b) through (d) of this section. Information relating to samples and labeling, described in paragraph (e) of this section, is required to be submitted in hard copy. Tabulations of patient data and case report forms, described in paragraph (f) of this section, may be submitted on microfiche only if the applicant and FDA agree. If FDA agrees, the applicant may use another suitable microform system.

(2) The applicant shall submit a review copy of the application. Each of the technical sections (described in paragraph (d) (1) through (6) of this section) in the review copy is required to be separately bound with a copy of the application form required under paragraph (a) of this section and a copy of the summary required under paragraph (c) of this section. The applicant may obtain from FDA sufficient folders to bind the archival and review copies of the application.

§ 314.55 Abbreviated application.

(a) An abbreviated application is an application in which reports of nonclinical laboratory studies and reports of clinical investigations (except those pertaining to in vivo bioavailability of the drug product) may be omitted. The information may be omitted when the Food and Drug Administration has determined that the information already available to it is adequate to establish that a particular dosage form of a drug meets the statutory standards for safety and effectiveness. An abbreviated application will usually be reserved for duplicates of drug products previously approved under a full application under § 314.50. An abbreviated application is not required to comply with the requirements in § 314.50 (c), (d)(2), (4), (5), (6), and (f).

(b) FDA will file an abbreviated application only if it has made a finding that an abbreviated application is suitable for a drug product. If FDA finds that a drug product may be approved for marketing on the basis of an abbreviated application, it will make that finding publicly available, as follows:

(1) If the finding applies to a broad category of drug products, the agency will amend § 314.56 to identify the category in that section.

(2) If the finding applies to a drug product because it is so closely related to a product for which an abbreviated application is suitable that the same conclusions about safety and effectiveness apply to it, the agency will make the finding public by updating its list of drug products for which abbreviated applications are suitable. The list is available from the National Technical Information Service, Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161.

(3) If the finding applies to duplicates of a drug product that is subject to FDA's Drug Efficacy Study Implementation program (a review of drug products approved as safe between 1938 and 1962), the agency will make that finding public through a notice published in the Federal Register.

(c)(1) A finding by FDA that an abbreviated application is suitable for a drug product applies only to a product that is the same in active ingredient, dosage form and strength, route of administration, and conditions of use as the drug product that was the subject of the finding. For drug product that is similar but different in one or more of these characteristics, an abbreviated application will be accepted only if FDA has made a separate finding of suitability. However, filing of an abbreviated application for a drug product does not signify that the product is safe and effective until the application is approved.

(2) A finding that a drug product is a new drug because it is similar to a product that is a new drug, and is therefore subject to the requirements of this part, does not include a finding that an abbreviated application is suitable for the similar product.

(3) A finding that a single-active-entity drug product is safe and effective and that an abbreviated application is suitable is not a basis for determining that a combination drug product containing that entity as one of its ingredients is either safe or effective or that an abbreviated application is suitable. The finding also is not a basis for determining that the combination drug product meets all of the requirements for combination drugs as described in § 300.50.

(d) (1) A person may seek a determination of the suitability of an abbreviated application for a product that the person believes is similar or related to a drug product that has been declared to be suitable for an abbreviated application. Extension of the finding that a drug product is safe and effective to another product will ordinarily be limited to other dosage forms for the same route of administration or to closely related ingredients. If preclinical or clinical evidence is needed to support the safety, or if clinical evidence is needed to support the effectiveness, of the proposed product, then an abbreviated application is not appropriate for the similar or related drug product.

(2) A person seeking a determination that an abbreviated application is suitable for a similar or related drug product shall use the petition procedures established in § 10.30. The petitioner shall set forth the reasons that justify extending the finding that an abbreviated application is suitable for one product to the similar or related product proposed to be marketed.

(3) An application submitted in the form of an abbreviated application for a drug product that has not been the subject of a finding that allows an abbreviated application for the product will be considered to be a petition under § 10.30 and will be processed as such.

(e) Each abbreviated application is required to contain a reference to FDA's finding that an abbreviated application is suitable for the specific product that is the subject of the application and to contain both an archival and a review copy of the application.

(1) The applicant shall submit a complete archival copy of the application that contains the information required under § 314.50 (a), (b), (d)(1) and (3), (e), and (g). An applicant may submit the archival copy of the application on microfiche or, if FDA agrees, another suitable microform system.

(2) The applicant shall submit a review copy that contains the technical sections described in § 314.50(d)(1) and (3). Each of the technical sections in the review copy is required to be separately bound with a copy of the application form required under § 314.50(a).

(3) The applicant may obtain from FDA sufficient folders to bind the archival and the review copies of the application.

§ 314.56 Drug products for which abbreviated applications are suitable.

Abbreviated applications are suitable for the following drugs within the limits set forth in § 314.55(c):

(a) Duplicates of drug products that were first approved before October 10, 1962, and reformulations of these products, if the original or reformulated product has been evaluated as part of the drug efficacy study and announced by notice in the Federal Register as effective for one or more indications, and if the Food and Drug Administration has made a finding that an abbreviated application is suitable.

(b) [Reserved]

(c) Drug products that are very closely related to a product described in paragraph (a) of this section and that are subject to a separate finding of suitability for marketing under an abbreviated application.

(d) Drug products that contain a chlorofluorocarbon determined to be an essential use and identified in § 2.125(h)(2) as suitable for an abbreviated application.

(e) Duplicates of an antibiotic drug for which FDA has approved an application.

§ 314.60 Amendments to an unapproved application.

The applicant may submit an amendment to an application that is filed under § 314.100, but not yet approved. The submission of a major amendment (for example, an amendment that contains significant new data from a previously unreported study or detailed new analyses of previously submitted data), whether on the applicant's own initiative or at the invitation of the agency, constitutes an agreement by the applicant under section 505(c) of the act to extend the date by which the agency is required to reach a decision on the application. Ordinarily, the agency will extend the review period for a major amendment but only for the time necessary to review the new information. However, the agency may not extend the review period more than 180 days. If the agency extends the review period for the application, the director of the division responsible for reviewing the application will notify the applicant of the length of the extension. The submission of an amendment that is not a major amendment will not extend the review period.

§ 314.65 Withdrawal by the applicant of an unapproved application.

An applicant may at any time withdraw an application that is not yet approved by notifying the Food and Drug Administration in writing. The agency will consider an applicant's failure to respond within 10 days to an approvable letter under § 314.110 or a not approvable letter under § 314.120 to be a request by the applicant to withdraw the application. A decision to withdraw the application is without prejudice to refiling. The agency will retain the application and will provide a copy to the applicant on request under the fee schedule in § 20.42 of FDA's public information regulations.

§ 314.70 Supplements and other changes to an approved application.

(a) *Changes to an approved application.* The applicant shall notify the Food and Drug Administration about each change in each condition established in an approved application beyond the variations already provided for in the application. The notice is required to describe the change fully. Depending on the type of change, the applicant shall notify FDA about it in a supplemental application under paragraph (b) or (c) of this section or by inclusion of the information in the annual report to the application under paragraph (d) of this section. Notwithstanding the requirements of paragraphs (b) and (c) of this section, an applicant shall make a change provided for in those paragraphs (for example, the deletion of an ingredient common to many drug products) in accordance with a guideline, notice, or regulation published in the Federal Register that provides for a less burdensome notification of the change (for example, by notification at the time a supplement is submitted or in the next annual report).

(b) *Supplements requiring FDA approval before the change is made.* An applicant shall submit a supplement, and obtain FDA approval of it, before making the changes listed below in the conditions in an approved application, unless the change is made to comply with an official compendium. An applicant may ask FDA to expedite its review of a supplement if a delay in making the change described in it would impose an extraordinary hardship on the applicant. Such a supplement and its mailing cover should be plainly marked: "Supplement -- Expedited Review Requested."

(1) *Drug substance.* A change affecting the drug substance to accomplish any of the following:

(i) To relax the limits for a specification;

(ii) To establish a new regulatory analytical method;

(iii) To delete a specification or regulatory analytical method;

(iv) To change the synthesis of the drug substance, including a change in solvents and a change in the route of synthesis.

(v) To use a different facility or establishment to manufacture the drug substance, where: (*a*) the manufacturing process in the new facility or established differs materially from that in the former facility or establishment, or (*b*) the new facility or establishment has not received a satisfactory current good manufacturing practice (CGMP) inspection within the previous 2 years covering that manufacturing process.

(2) *Drug product.* A change affecting the drug product to accomplish any of the following:

(i) To add or delete an ingredient, or otherwise to change the composition of the drug product, other than deletion of an ingredient intended only to affect the color of the drug product;

(ii) To relax the limits for a specification;

(iii) To establish a new regulatory analytical method;

(iv) To delete a specification or regulatory analytical method;

(v) To change the method of manufacture of the drug product, including changing or relaxing an in-process control;

(vi) To use a different facility or establishment, including a different contract laboratory or labeler, to manufacture, process, or pack the drug product;

(vii) To change the container and closure system for the drug product (for example, glass to high density polyethylene (HDPE), or HDPE to polyvinyl chloride) or change a specification or regulatory analytical method for the container and closure system;

(viii) To change the size of the container, except for solid dosage forms, without a change in the container and closure system.

(ix) To extend the expiration date of the drug product based on data obtained under a new or revised stability testing protocol that has not been approved in the application.

(x) To establish a new procedure for reprocessing a batch of the drug product that fails to meet specifications.

(3) *Labeling.* Any change in labeling, except one described in paragraph (c)(2) or (d) of this section.

(c) *Supplements for changes that may be made before FDA approval.* An applicant shall submit a supplement at the time the applicant makes any kind of change listed below in the conditions in an approved application, unless the change is made to comply with an official compendium. A supplement under this paragraph is required to give a full explanation of the basis for the change, identify the date on which the change is made, and, if the change concerns labeling, include 12 copies of final printed labeling. The applicant shall promptly revise all promotional labeling and drug advertising to make it consistent with any change in the labeling. The supplement and its mailing cover should be plainly marked: "Special Supplement -- Changes Being Effected."

(1) Adds a new specification or test method or changes in the methods, facilities (except a change to a new facility), or controls to provide increased assurance that the drug will have the characteristics of identity, strength, quality, and purity which it purports or is represented to possess;

(2) Changes labeling to accomplish any of the following:

(i) To add or strengthen a contraindication, warning, precaution, or adverse reaction;

(ii) To add or strengthen a statement about drug abuse, dependence, or overdosage; or

(iii) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the product.

(iv) To delete false, misleading, or unsupported indications for use or claims for effectiveness.

(3) To use a different facility or establishment to manufacture the drug substance, where: (i) The manufacturing process in the new facility or establishment does not differ materially from that in the former facility or establishment, and (ii) the new facility or establishment has received a satisfactory current good manufacturing practice (CGMP) inspection within the previous 2 years covering that manufacturing process.

(d) *Changes described in the annual report.* An applicant shall not submit a supplement to make any change in the conditions in an approved application, unless otherwise required under paragraph (b) or (c) of this section, but shall describe the change in the next annual report required under § 314.81. Some examples of changes that can be described in the annual report are the following:

(1) Any change made to comply with an official compendium.

(2) A change in the labeling concerning the description of the drug product or in the information about how the drug product is supplied, that does not involve a change in the dosage strength or dosage form.

(3) An editorial or similar minor change in labeling.

(4) The deletion of an ingredient intended only to affect the color of the drug product.

(5) An extension of the expiration date based upon full shelf-life data obtained from a protocol approved in the application.

(6) A change within the container and closure system for the drug product (for example, a change from one high density polyethylene (HDPE) to another HDPE), except a change in container size for nonsolid dosage forms, based upon a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium.

(7) The addition or deletion of an alternate analytical method.

(8) A change in the size of a container for a solid dosage form, without a change from one container and closure system to another.

§ 314.71 Procedures for submission of a supplement to an approved application.

(a) Only the applicant may submit a supplement to an application.

(b) All procedures and actions that apply to an application under § 314.50 and an abbreviated application under § 314.55 also apply to supplements, except that the information required in the supplement is limited to that needed to support the change. A supplement is required to contain an archival copy and a review copy that include an application form and appropriate technical sections, samples, and labeling.

(c) All procedures and actions that apply to applications under this part, including actions by applicants and the Food and Drug Administration, also apply to supplements.

§ 314.72 Change in ownership of an application.

(a) An applicant may transfer ownership of its application. At the time of transfer the new and former owners are required to submit information to the Food and Drug Administration as follows:

(1) The former owner shall submit a letter or other document that states that all rights to the application have been transferred to the new owner.

(2) The new owner shall submit an application form signed by the new owner and a letter or other document containing the following:

(i) The new owner's commitment to agreements, promises, and conditions made by the former owner and contained in the application;

(ii) The date that the change is ownership is effective; and

(iii) Either a statement that the new owner has a complete copy of the approved application, including supplements and records that are required to be kept under § 314.81, or a request for a copy of the application from FDA's files. FDA will provide a copy of the application to the new owner under the fee schedule in § 20.42 of FDA's public information regulations.

(b) The new owner shall advise FDA about any change in the conditions in the approved application under § 314.70, except the new owner may advise FDA in the next annual report about a change in the drug product's label or labeling to change the product's brand or the name of its manufacturer, packer, or distributor.

§ 314.80 Postmarketing reporting of adverse drug experiences.

(a) *Definitions.* The following definitions of terms apply to this section:

"Adverse drug experience" means any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: an adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose, whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any significant failure of expected pharmacological action.

"Increased frequency" means an absolute increase in the number of reports of an adverse drug experience received during a specified time period compared to the number of similar adverse drug experience reports received during an equivalent time period in the past.

"Serious" means an adverse drug experience that is life threatening, is permanently disabling, requires inpatient hospitalization, or requires prescription drug therapy. In addition, an adverse drug experience with one of the following outcomes is always considered serious: death, congenital anomaly, cancer, or overdose.

"Unexpected" means an adverse drug experience that is not listed in the current labeling for the drug and includes an event that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differs from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents.

(b) *Review of adverse drug experiences.* Each applicant having an approved application under § 314.50 or § 314.55 shall promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers.

(c) *Reporting requirements.* The applicant shall report to FDA adverse drug experience information, as described in this section. The applicant shall submit two copies of each report described in this section to the Division of Drug and Biological Product Experience (HFN-70), Center for Drugs and Biologics, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. FDA may waive the requirement for the second copy in appropriate instances.

(1) *Fifteen-day "Alert reports."* (i) The applicant shall report each adverse drug experience that is both serious and unexpected, regardless of source, as soon as possible but in any case within 15 working days of initial receipt of the information. These reports are required to be submitted on Form FDA-1639 (Drug Experience Report). The applicant shall promptly investigate all adverse drug experiences that are the subject of these 15-day Alert reports and shall submit followup reports within 15 working days of receipt of new information or as requested by FDA. If additional information is not obtainable, a followup report may be required that describes briefly the steps taken to seek additional information and the reasons why it could not be obtained. These 15-day Alert reports and followups to them are required to be submitted under separate cover and may not be included, except for summary or tabular purposes, in a periodic report.

(ii) The applicant shall review periodically (at least as often as the periodic reporting cycle) the frequency of reports of adverse drug experiences that are both serious and expected, regardless of source, and report any significant increase in frequency as soon as possible but in any case within 15 working days of determining that a significant increase in frequency exists. Upon written notice, FDA may require that applicants review the frequency of reports of serious, expected adverse drug experiences at intervals different than the periodic reporting cycle. Reports of a significant increase in frequency are required to be submitted in narrative form (including the time period on which the increased frequency is based, the method of analysis, and the interpretation of the results), rather than using Form FDA-1639. Fifteen-day Alert reports based on increased frequency are required to be submitted under separate cover and may not be included, except for summary purposes, in a periodic report.

(iii) The requirements of paragraph (c)(1) (i) and (ii) of this section, concerning the submission of 15-day alert reports, shall also apply to any person (other than the applicant) whose name appears on the label of an approved drug product as a manufacturer, packer, or distributor. However, in order to avoid unnecessary duplication in the submission to FDA, and followup to, reports required by paragraph (c)(1) (i) and (ii) of this section, obligations of a nonapplicant may be met by submission of all reports of serious adverse drug experiences to the applicant. If a nonapplicant elects to submit adverse drug experience reports to the applicant rather than to FDA, it shall submit each report to the applicant

within 3 working days of its receipt by the nonapplicant, and the applicant shall then comply with the requirements of this section. Under this circumstance, the nonapplicant shall maintain a record of this action which shall include:

(*a*) A copy of the drug experience report.

(*b*) Date the report was received by the nonapplicant.

(*c*) Date the report was submitted to the applicant.

(*d*) Name and address of the applicant.

(iv) Each report submitted under this paragraph shall bear prominent identification as to its contents, i.e., "15-day Alert report" or "15-day Alert report -- followup."

(2) *Periodic adverse drug experience reports.* (i) The applicant shall report each adverse drug experience not reported under paragraph (c)(1)(i) of this section at quarterly intervals, for 3 years from the date of approval of the application, and then at annual intervals. The applicant shall submit each quarterly report within 30 days of the close of the quarter (the first quarter beginning on the date of approval of the application) and each annual report within 60 days of the anniversary date of approval of the application. Upon written notice, FDA may extend or reestablish the requirement that an applicant submit quarterly reports, or require that the applicant submit reports under this section at different times than those stated. For example, the agency may reestablish a quarterly reporting requirement following the approval of a major supplement. Followup information to adverse drug experiences submitted in a periodic report may be submitted in the next periodic report.

(ii) Each periodic report is required to contain: (*a*) a narrative summary and analysis of the information in the report and an analysis of the 15-day Alert reports submitted during the reporting interval (all 15-day Alert reports being appropriately referenced by the applicant's patient identification number, adverse reaction term(s), and date of submission to FDA); (*b*) a Form FDA-1639 (Drug Experience Report) for each adverse drug experience not reported under paragraph (c)(1)(i) of this section (with an index consisting of a line listing of the applicant's patient identification number and adverse reaction term(s); and (*c*) a history of actions taken since the last report because of adverse drug experiences (for example, labeling changes or studies initiated).

(iii) Periodic reporting, except for information regarding 15-day Alert reports, does not apply to adverse drug experience information obtained from postmarketing clinical trials (whether or not conducted under an investigational new drug application), from reports in the scientific literature, and from foreign marketing experience.

(d) *Scientific literature.* (1) A 15-day Alert report based on information from the scientific literature is required to be accompanied by a copy of the published article. The 15-day reporting requirements in paragraph (c)(1)(i) of this section (i.e., serious, unexpected adverse drug experiences) apply only to reports found in scientific and medical journals either as case reports or as the result of a formal clinical trial. The 15-day reporting requirements in paragraph (c)(1)(ii) of this section (i.e., a significant increase in frequency of a serious, expected adverse drug experience) apply only to reports found in scientific and medical journals either as the result of a formal clinical trial, or from epidemiologic studies or analyses of experience in a monitored series of patients.

(2) As with all reports submitted under paragraph (c)(1)(i) of this section, reports based on the scientific literature shall be submitted on Form FDA-1639 or comparable format as prescribed by paragraph (f) of this section. In cases where the applicant believes that preparing the Form FDA-1639 constitutes an undue hardship, the applicant may arrange with the Division of Drug and Biological Product Experience for an acceptable alternative reporting format.

(e) *Postmarketing epidemiological/surveillance studies.* Adverse drug experiences from postmarketing epidemiological/surveillance studies, except for 15-day Alert reports, may be submitted following the completion of the study in the next periodic report. (A study is considered completed 1 year after it is concluded.) The applicant shall separate and clearly mark reports of adverse drug experiences that occur during such a postmarketing study as being distinct from those experiences that are being reported spontaneously to the applicant. Applicants are encouraged to submit such reports utilizing an alternative format to Form FDA-1639, as provided in paragraph (f)(3) of this section.

(f) *Reporting Form FDA-1639.* (1) Except as provided in paragraphs (c)(1)(ii) and (f)(3) of this section, the applicant shall complete a Form FDA-1639 (Drug Experience Report) for each report of an adverse drug experience.

(2) Each completed Form FDA-1639 should refer only to an individual patient or a single attached publication.

(3) Instead of using Form FDA-1639, an applicant may use a computer-generated FDA-1639 or other alternative format (e.g., a computer-generated tape or tabular listing) provided that: (i) The content of the alternative format is equivalent in all elements of information to those specified in Form FDA-1639; and (ii) the format is agreed to in advance by the Division of Drug and Biological Experience (HFN-730).

(4) Single copies of Form FDA-1639 may be obtained from the Division of Drug and Biological Product Experience (HFN-730), Center for Drugs and Biologics, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Supplies of Form FDA-1639 may be obtained from the PHS Forms and Publications Distribution Center, 12100 Parklawn Dr., Rockville, MD 20857.

(g) *Multiple reports.* An applicant should not include in reports under this section any adverse drug experiences that occurred in clinical trials if they were previously submitted as part of the approved application. If a report applies to a drug for which an applicant holds more than one approved application, the applicant should submit the report to the application that was first approved. If a report refers to more than one drug marketed by an applicant, the applicant should submit the report to the application for the drug listed first in the report.

(h) *Patient privacy.* An applicant should not include in reports under this section the names and addresses of individual patients; instead, the applicant should assign a unique code number to each report, preferably not more than eight characters in length. The applicant should include the name of the reporter from whom the information was received. Names of patients, health care professionals, hospitals, and geographical identifiers in adverse drug experience reports are not resaleable to the public under FDA's public information regulations in Part 20.

(i) *Recordkeeping.* The applicant shall maintain for a period of 10 years records of all adverse drug experiences known to the applicant, including raw data and any correspondence relating to adverse drug experiences.

(j) *Guideline.* FDA has prepared under § 10.90(b) a guideline for the submission of reports of adverse drug experiences and suggested followup investigation of reports.

(k) *Withdrawal of approval.* If an applicant fails to establish and maintain records and make reports required under this section, FDA may withdraw approval of the application and, thus, prohibit continued marketing of the drug product that is the subject of the application.

(l) *Disclaimer.* A report or information submitted by an applicant under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the applicant or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse effect. An applicant need not admit, and may deny, that the report or information submitted under this section constitutes an admission that the drug caused or contributed to an adverse effect. For purposes of this provision, the term "applicant" also includes any person reporting under paragraph (c)(1)(iii) of this section.

§ 314.81 Other postmarketing reports.

(a) *Applicability.* Each applicant shall make the reports for each of its approved applications and abbreviated applications required under this section and sections 505(j) and 507(g) of the act.

(b) *Reporting requirements.* The applicant shall submit to the Food and Drug Administration at the specified times two copies of the following reports:

(1) *NDA -- Field alert report.* The applicant shall submit information of the following kinds about distributed drug products and articles to the FDA district office that is responsible for the facility involved within 3 working days of receipt by the applicant. The information may be provided by telephone or other rapid communication means, with prompt written followup. The report and its mailing cover should be plainly marked: "NDA -- Field Alert Report."

(i) Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article.

(ii) Information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specifications established for it in the application.

(2) *Annual report.* The applicant shall submit the following information in the order listed each year within 60 days of the anniversary date of approval of the application. The applicant shall submit the report to the FDA division responsible for reviewing the application. Each annual report is required to be accompanied by a completed transmittal Form